



SOLUBILITY ENHANCEMENT TECHNIQUES

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ABSTRACT

The phenomena of solubility, in which a solid dissolves in a liquid to form a uniform system, is known as the phase transition. Solubility is one of the critical parameter to attain required concentration of medication in systemic circulation for pharmacological response to be displayed. Poorly water-soluble medicines may need large dosages in order to attain therapeutic plasma concentrations following oral delivery. Low aqueous solubility is the fundamental difficulty faced with formulation creation of novel chemical entities. Any medicine to be absorbed must be present in the form of an aqueous solution at the site of absorption. Liquid pharmaceutical formulations often use water as their solvent. Most pharmaceuticals have a neutral pH and are hardly soluble in water. Hence different strategies are utilised for the enhancement of the solubility of poorly water-soluble pharmaceuticals including micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, micellar solubilization, hydrotropy etc. The goal of this review article is to discuss the strategies of solubilization for the accomplishment of efficient absorption and increased bioavailability.

KEYWORDS: Solubility, solubility enhancement, co-solvent, pH, emulsions.

INTRODUCTION

It is possible to increase the bioavailability of a medicine that is poorly water soluble by adapting a variety of methods for solubilizing the molecule. Methods including micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, micellar solubilization, hydrotropy, etc. are often used to dissolve drugs. When conducting screening investigations of novel chemical entities or when designing and developing formulations, solubilization of poorly soluble pharmaceuticals is a common obstacle.^[1,2] An aqueous solution of the medication must be present at the absorption site.^[3-6] Because solubility and permeability determine how well a medicine is absorbed in the body, they may be improved using methods such.^[7] The greatest quantity of solute that may be dissolved in a given amount of solvent is the definition of the word "solubility." Quality and quantity both work for defining it. Quantitatively it is defined as the concentration of the solute in a saturated solution at a specific temperature. Solubility, in a qualitative sense, may be described as the spontaneous interaction between two or more substances to generate a homogeneous molecular dispersion. A saturated solution is one in which the solute is in equilibrium with the solvent. The solubility of a medicine is indicated by different concentration expression such as parts, percentage,

molarity, molality, volume fraction, mole fraction.^[8-10] Thus, the first section of this study focuses on the conventional methods of drug solubilization, such as changing the pH, using a cosolvent, and decreasing the particle size. However, self-emulsifying and microemulsion systems are innovative new methods. The many ways of solubility improvement are explained here.

pH ADJUSTMENT

It is possible that a change in pH might aid in the dissolution of medications that are poorly water soluble but include sections of the molecule that can be protonated (base) or deprotonated (acid). In theory, modifying the pH of a drug may be utilised for both oral and intravenous dosing. Because blood is a powerful buffer with a pH between 7.2 and 7.4, a poorly soluble medication may precipitate after intravenous injection. The buffer capacity and tolerance of the chosen pH are crucial factors in determining the approach's viability. When a medicine is taken orally, its level of solubility is likely to change as it travels through the intestines, where the pH ranges from around 1 to 2 in the stomach to about 5 to 7.5 in the duodenum. The optimal candidates are ionizable chemicals that are stable and soluble following pH adjustment. The compounds might be acidic, basic,

or zwitterionic. It may be used for both crystalline and lipophilic poorly soluble substances.^[11-14]

Increasing the pH of the environment within a dosage form (tablet or capsule) to a value greater than the pKa of a weakly-acidic medicine improves the solubility of that drug, whereas excipients that function as alkalinizing agents may improve the solubility of weakly basic pharmaceuticals.^[15,16]

If chemicals may pass through the epithelium orally, the proportion of orally absorbed medicine may rise because the solubility of the poorly soluble drug is improved in comparison to water alone. Increasing the solubility of a poorly soluble medication sometimes requires combining pH modification with co-solvents. Bioavailability may be improved if the precipitate after dilution is fine or amorphous, since this creates a steeper concentration gradient and more dissolvable surface area. The drug's bioavailability may not be adequately improved if it precipitates into poorly soluble particles that need to be dissolved and do not promptly redissolve. Since pre-clinical pH modification is a suitable tool to evaluate the effectiveness of poorly soluble medications, this method is widely used in Survey. However, findings may be misinterpreted if the poorly soluble medication precipitates unpredictably after being exposed to a pH at which it is significantly less soluble (oral and parenteral). Its benefits include its ease of formulation, analysis, production, and quick tracking. • Only requires a little amount of the drug, allowing for rapid testing at scale. Disadvantages: • Possibility of precipitation when diluted with aqueous solutions of a lower pH, where the chemical is less soluble. When administered intravenously, it may produce emboli; when taken orally, it can cause variation. • The effects of using non-physiological and very acidic or basic pH on tolerance and toxicity (both local and systemic). • A medicine that has been dissolved in water is often chemically less stable than crystalline solid formulations, as is the case with all solubilized and dissolved systems. Hydrolysis or other types of degradation might be sped up depending on the chosen pH. In the business world, pH-adjustable items include: A formulation including co-solvents that has had its pH adjusted is the 50 mg/ml phenytoin injection (Epanutin® ready mixed, Pfizer), which contains 40% propylene glycol and 10% ethanol (1.1 mmol Na⁺ per 5 ml ampoule).

CO-SOLVENCY

Adding a cosolvent, or a solvent that is miscible with water and in which the medication is soluble, may often boost the drug's solubility in water.^[17] Combinations of water and other solvents that are miscible with water are called co-solvents, and they are used to make solutions of chemicals that are otherwise difficult to dissolve. Because it is so easy to use and assess, this method has seen extensive application throughout history. PEG 300, propylene glycol, and ethanol are all solvents that are often employed in co-solvent combinations. Co-solvent

formulations allow both oral and parenteral administration of poorly soluble medicines. It is common practise to dilute parenteral formulations with water or another aqueous solution before delivery. In the pharmaceutical industry, the product is always administered in a liquid form. A co-solvent strategy may be useful for solubilizing chemicals that are poorly soluble on their own but are extremely crystalline or lipophilic.

When compared to the solubility of the medicine in water, the use of a co-solvent may boost the solubility of weakly soluble molecules by a factor of several thousand. As opposed to previous solubilization methods, very high drug concentrations of weakly soluble substances may be dissolved. Bioavailability may not improve much, however, since poorly soluble drugs tend to precipitate out of solution in an unpredictably crystalline or amorphous form upon dilution. To be absorbed orally, this precipitate must first be dissolved. Poorly soluble chemicals may be made more soluble with the use of co-solvents, in addition to conventional solubilization strategies, such as pH change. To improve the solubility of poorly soluble medicines, co-solvents are often used.^[18-20] For parenteral administration, propylene glycol, ethanol, glycerin, and polyethylene glycol are the most often utilised low toxicity cosolvents. 21-24 Given their considerable solubilization capacity for poorly soluble medicines and their low toxicity, dimethylsulfoxide (DMSO) and dimethylacetamide (DMA) have been frequently employed as cosolvents.^[25-27]

The benefits include: • being easy to develop and manufacture quickly.

Cons: • As is the case with all excipients, the toxicity and tolerability associated with the amount of solvent provided must be taken into account. • Unpredictable precipitation forms when mixed with water. The precipitates may range in size and can be either amorphous or crystalline. Intravenous delivery, in particular, is not a good fit for many of the less soluble chemicals that Phares works with. The medications precipitate out of the co-solvent combination and are very difficult to re-dissolve in water. Embolism and local adverse effects at the injection site are possibilities in these scenarios. • The chemical stability of the insoluble drug is lower in a solubilized form, as it is in all solubilized forms. Product examples of co-solvent formulations are Nimodipine Intravenous Injection (Nimotop®, Bayer) and Digoxin Elixir Pediatric (Lanoxin®, GSK).

Particle Size Reduction

The bioavailability inherently connected to medication particle size. A better dissolving rate may be achieved by decreasing particle size and increasing the surface area. Milling processes, such the jet mill and the rotor stator colloid mills, are used to decrease particle size. Because

it does not alter the drug's saturation solubility, it is not appropriate for high-dose medicines.^[28] Nowadays Both micronization and nanosuspension may reduce particle size to an acceptable level. Particle size reduction equipment varies across methods. In micronization the solubility of medicine is typically fundamentally connected to drug particle size. By lowering the particle size, the increased surface area increases the dissolving capabilities of the medication. Milling methods such as jet mill, rotor stator colloid mills, etc. are used for the micronization of pharmaceuticals. Micronization is not ideal for medications with a high dosage number since it does not modify the saturation solubility of the drug. An other method, known as nanosuspension, involves the sub-micron colloidal dispersion of pure drug particles stabilised by surfactants. The nanosuspension method has been applied for pharmaceuticals like tarazepide, atovaquone, amphotericin B, paclitaxel and bupravaquon. The benefits afforded by nanosuspension include enhanced dissolving rate is related to bigger surface area exposed, while lack of Ostwald ripening is due to the homogenous and limited particle size range achieved, which removes the concentration gradient effect. Nanosuspensions are created via homogenization and wet milling technique.

CONCLUSION

This article concludes that medication solubility is the most significant aspect in formulation creation since it directly affects both the drug's formulation and its therapeutic effectiveness. Solubility is a prerequisite for the formulation and development of multiple dosage forms of different pharmaceuticals, and the rate at which a drug dissolves in water is a key factor in oral absorption of poorly water-soluble drugs. The various techniques described above alone or in combination can be used to enhance the solubility of the drug. Multiple methods exist to boost solubility, and in some cases the increase may be as high as a thousandfold. Many medications' bioavailability is reduced due to their insolubility, making solubility improvement a need. Poorly soluble medications may currently be made more soluble by the use of the aforementioned methods.

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